Official title: A Comparison of Epidural and Intravenous Patient Control Analgesia Following Lumbar Spinal Fusion Surgery: A Prospective Randomized Study

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Protocol

Title: A Comparison of Epidural and Intravenous Patient Control Analgesia Following Lumbar Spinal Fusion Surgery: A Prospective Randomized Study

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1. Introduction and Purpose – Postoperative analgesia following spine surgery is difficult to manage. Current treatment modalities rely heavily on opioid analgesics with all of the inherent limitations and side effects. While current best practice focuses on a 'multimodal approach' (i.e. using multiple different drugs and techniques to control pain after surgery), there is no consensus regarding which components of this multimodal therapy provide optimal analgesia. This prospective randomized study will enroll patients undergoing elective Lumbar Spinal Fusion Surgery at Zale Lipshy University Hospital. The primary objective is to determine the comparative efficacy of epidural analgesia, as compared with intravenous (IV) patient-controlled analgesia (PCA), on post-operative analgesia.

Hypothesis1: We hypothesize that patients undergoing Lumbar Spinal Fusion surgery with epidural catheter placement will have superior post-operative analgesia compared to patients receiving IV PCA.
Specific Aim1: Patient received PCEA will have lower Visual Analog pain sores (VAS) at 24 hour postoperatively compared to those who received IV PCA.
Primary outcome measure: Postoperative VAS score at 24 hours

Hypothesis2: Epidural analgesia with intraoperative epidural catheter may decrease postoperative opioid consumption compared to IV PCA.
Specific Aim2: Patients received PCEA with intraoperative epidural catheter will consume less opioid during the first 24-h postoperative period compared to those who received IV PCA.
Secondary outcome measure: Postoperative opioid consumption within the first 24 hours.

2. Background & Significance – Low back pain is one of the most prevalent debilitating musculoskeletal conditions in the United States. (1) Therefore, lumbar spine surgery is a commonly performed procedure in the United States. Many patients undergoing lumbar spine surgery have chronic pain syndromes pre-operatively which can present challenges in the treatment of post-operative pain. The importance of adequate post-operative pain control has recently been emphasized with the awareness that inadequate treatment may result in a higher incidence of the development of chronic post-surgical pain and increase post-operative comorbidities. (2) Multiple drugs and protocols for the treatment of post-operative pain

following lumbar spine surgery have been studied, but no best method has been shown to date. (3)

Most studies of lumbar spine surgery pain management have investigated comparisons between intravenous opioids, intrathecal local anesthetics and opioids, and epidural local anesthetics and opioids. There have been mixed results regarding the superior approach to post-operative pain management and complications. (4-7) Several of these conflicting studies contain small sample sizes and have various other limitations. Therefore, further investigation is warranted to improve post-operative pain control following lumbar spine surgery. The current study seeks to improve care of patients in the UT Southwestern Spine Center by comparing intravenous patient-controlled opioid analgesia versus continuous epidural analgesia. There are several potential advantages to epidural therapy. These include decreased opioid use leading to fewer side effects such as respiratory depression, nausea, ileus, and sedation. (8) Epidural analgesia has also been shown to provide better post-operative analgesia when compared to parenteral opioids in a variety of surgical procedures and with a variety of analgesic agents. (2)

Ilangovan et al (2017) used intraoperatively placed epidural catheter for postoperative pain relief after spinal fusion surgery in terms of efficacy and cost. The investigators used epidural tramadol and concluded that epidural intraoperative placement of the epidural catheter is a simple way of delivering medication to the epidural space. Li at al. (2015) compared outcome of PCEA and IV PCA after spinal fusion surgery. According to their results PCEA showed significantly greater efficacy than IV PCA for pain management after spinal fusion surgery, with lower VAS scores, higher frequency of recovery activities, and overall higher satisfaction level. They also monitored adverse effects of PCEA and IV PCA, which includes nausea, vomiting, pruritus, drowsiness, respiratory depression, and headache. In the IV PCA group, the incidence of hypopiesia and skin itching were higher with markedly lower drowsiness and headache when compared to the PCEA group. In the current meta-analyses of randomized clinical trials, Lu et al (2015) compared the efficacy and safety of PCEA and IV PCA in postoperative analgesia of spinal fusion surgery. They showed that the analgesic effect on patients in the PCEA group was better than that in the IV PCA group on the first and second postoperative days without significant difference in analgesic effects on the third postoperative day after spinal fusion. In a randomized prospective clinical trial, efficacy of postoperative analgesia was evaluated in patients with adolescent idiopathic scoliosis undergoing posterior spinal fusion. PCEA effectively controlled postoperative pain with the fewest side effects (Klatt et al. 2013).

Cassady et al (2000) compared continuous thoracic epidural analgesia and patient-controlled analgesia in postoperative care of adolescents with idiopathic scoliosis and observed significantly more rapid return of bowel sounds in PCEA group. Turner et al (2000) evaluated intraoperative placement of epidural catheter under direct visualization of the surgeon on 14 consecutive cases undergoing spinal fusion surgery and had epidural radio-opaque dye injected 15 minutes before their postoperative chest X-ray. Seven patients had visible dye in epidural space, and all these cases had satisfactory analgesia. According to this small pilot study, correctly placed epidural catheters are capable of providing good postoperative analgesia for posterior spinal surgery. Cata et al (2008) retrospectively reviewed 245 medical records of adult patients undergoing major spine surgery who received either patient-controlled epidural analgesia based on local anesthetics and opioids or patient-controlled intravenous analgesia as

postoperative pain management. They showed a reduced amount of opioids with epidural analgesia, which may decrease potential side effects mainly in elderly patients.

In a prospective, double-blind, randomized clinical trial, Schenk et al (2006) investigated the efficacy of PCEA compared with IV PCA and concluded that PCEA with ropivacaine and sufentanil, using intraoperatively placed epidural catheters, provides superior analgesia and higher patient satisfaction when compared with PCIA after spinal fusion surgery. Gottschalk et al (2004) evaluated 72 patients with intraoperative epidural catheter placement for postoperative analgesia for anterior-posterior spinal fusion surgery. They observed lower levels of pain at rest and during mobilization in the PCEA when compared to the IV PCA group. Cohen et al. (2) compared fixed continuous epidural analgesia (bupivacaine 0.0625%) via intraoperatively placed epidural catheters two or three levels above the cephalad operative level with IV PCA (morphine 1 mg/mL) after major spine surgery and found no differences in postoperative pain levels. The authors concluded that the diluted local anesthetic may not have reached the operative field in sufficient amounts.

3. Concise Summary – Study Design: Prospective study of 58 subjects undergoing elective Lumbar Spinal Fusion (1-3 levels- posterior approach) at UTSW Zale Lipshy University Hospital with:

1. 29 subjects receiving Continuous Lumbar Epidural Analgesia (Patient-Controlled Epidural Analgesia- PCEA groups)

2. 29 subjects receiving IV PCA

Subjects will be randomly assigned one of the study groups either PCEA or IV PCA. Randomization protocol will be prepared according to level of the spinal fusion levels (1-3).

Study Interventions – The intervention to be evaluated in this study is epidural analgesia using an infusion of 0.0625% bupivacaine plus fentanyl 2mcg/ml. The Patient Controlled Epidural Analgesia (PCEA) pump will be programmed with the following settings:

- Bolus dose 5ml following emergence from general anesthesia (after clinical neurologic exam)
- Infusion 6-10 ml/hour; 2ml demand bolus every 20 minutes
- Max dose set for infusion over 4 hours + 6 boluses (12ml)
  (Example - infusion 5ml/hr.; max 32ml over 4 hours)

This infusion will continue into the post-operative period. The epidural infusion will be continued until it is appropriate to transition the patient to a regimen of oral pain medications. This is typically determined by the surgical team, and the Acute Pain Service (APS). Duration of epidural catheter will be 72 hours a postoperatively. The APS will discontinue the epidural infusion and remove the epidural catheter per standard protocol.

For subjects in the IV PCA group, the intervention will include post-operative IV PCA with Hydromorphone (PCA syringe 25 mg/50 mL; dose range is 0.05mg - 0.4 mg which may be change according to patient`s body habitus, age, etc.).

Epidural catheters will be placed by the spine surgeon under direct visualization intra-operatively prior to closing the surgical incision. Intra-operative epidural catheter placement by the spine surgeon will typically be done at the upper end of the dural exposure/laminectomy and the catheter will be pushed cephalad 5-10cm up the epidural space. For safety reasons, the subjects with dura damage during surgery will be excluded from the study because unpredictable amounts of the local anesthetic might reach the intrathecal space.

Epidurals will be assessed for efficacy/function in the recovery room post-operatively by the APS, and then daily on the floor post-operatively (unless contacted by the floor nurse regarding specific concerns). Subjects are assessed for sensory function provided by the epidural (typically by sensation to cold or sharp), motor function, and any side effects or complications from the epidural. Motor block will be quantified with the Bromage scale (0 _ free movements of legs and feet, 1 _ just able to flex the knees with free movement of the feet, 2 _ unable to flex the knees but with free movement of the feet, and 3 _ unable to move legs or feet). Subjects will be asked about sensory deficits and graded on scale 1 to 3 (1 intact sensation, 2_ partial sensation, and 3_ complete sensation lost).

Visual analog pain scale (VAS) will be used to evaluate degree of pain at, 24, 48, and 72 hours after surgery. If a subject reports inadequate pain control with an epidural and the APS deems the epidural to be non-functional or non-efficacious, then the catheter may be removed and the patient may be changed to an IV PCA at that time.

Additionally, both the IV PCA and the epidural PCEA groups may be given additional "rescue" pain medications as needed in the recovery room, and these may be continued through the post-operative period on the floor. Current standard of care is using multimodal analgesia including acetaminophen, COX-2 specific inhibitors, dexamethasone, etc. These rescue medications may include, but are not limited to: pregabalin, gabapentin, methocarbamol, oxycodone, hydrocodone, methadone, and acetaminophen.

Total study duration is approximately 50 days, which starts from operating room admission for spinal fusion surgery to the first follow-up visit after discharge. Postoperative data will be collected during hospital stay and at the first follow-up visit.

4. Study Procedures:

Monitoring:

Standard intraoperative monitoring (EKG, blood pressure, pulse oximetry, end-tidal carbon dioxide, and temperature) and anesthetic care will be used in both groups.

Surgical and anesthetic technique: All subjects will undergo a standardized general anesthetic for the operative procedure (see Appendix 1). The surgery and postoperative management will also be standardized. The difference between patient cohorts will be the use of epidural vs. intravenous analgesia for post-operative pain management. Both study groups will receive hydromorphone, which is a standard of care drug for post-operative pain. If the subject has a documented allergy or intolerance to hydromorphone, then a different opioid may be substituted in either the IV PCA or the epidural drug solution. The epidural study group will also receive Bupivacaine (local anesthetic) in combination with fentanyl. The intervention being tested in the current study is the route of analgesic medication—intravenous or epidural,

as well as the addition of bupivacaine in the epidural analgesic group. Note that bupivacaine contraindicated for intravenous use, and may have significant cardiac and neurologic sequelae if given intravenously. Therefore, it will be included only in the epidural analgesia group.

Epidurals that are evaluated and felt to be non-efficacious will be removed, and the subject will be changed to intravenous hydromorphone PCA. These subjects will be statistically analyzed primarily by intent to treat method, with possible secondary analysis, to be analyzed in an 'as treated group'. Investigators will not be blinded to treatment allocation due to the nature of the intervention. Subjects will be randomized to receive IV PCA or epidural PCEA.

The following **variables** will be evaluated to determine differences between Epidural Analgesia and Standard Care:

Preoperative Data Collection during preoperative outpatient clinic visit or preoperative period before the surgery

- ***VAS score***
- ***Baseline delirium assessment (the Confusion Assessment Method (CAM) and the Mini-Cognition assessment (MiniCog)***
- ***Hospital anxiety depression scores (HADS) will be evaluated- baseline (preop)***
- ***Pain will also be evaluated with McGill short form questionnaire-baseline (preop).***

Postoperative data collection during hospital stay:

- Post-operative Visual Analogue Pain (VAS) Score within 3 hours or PACU discharge, postoperative 24, 48, and 72 hours during infusion days (±2 hrs.) after surgery (Primary endpoint: VAS Score at 24h).
- Post-operative intravenous opioid consumption for postoperative days 1, 2, and 3 (converted to Morphine Equivalents).
- Total use of post-operative oral opioid consumption during hospital stay on postoperative day 3.
- Total use of breakthrough medication on postoperative day 3.
- Patient satisfaction score at the last infusion day or postoperative day 3 or at discharge if patient discharged before POD3.
- Delirium during the hospital stay. Patients will be assessed baseline (preop) and daily during epidural or IV infusion , and the 6-week follow-up using the Confusion Assessment Method (CAM) and the Mini-Cognition assessment.
- Epidurals will be assessed for efficacy/function in the recovery room post-operatively by the Acute Pain Service, and then daily during infusion days (24, 48, and 72 hours)
- Length of hospital stay.
- Nausea, vomiting and antiemetic use for postoperative 72 hours
- Time to first bowel movement after surgery
- Wound infection rates during hospital stay
- Time to first ambulation after surgery
- Adverse effects include nausea, vomiting, pruritus, drowsiness, respiratory depression, and headache etc.

Data collection during 6-week follow-up visit (approximately postoperative 50 days):

- VAS Score

- HADS
- Pain evaluation with McGill short form questionnaire
- Patient satisfaction with post-operative analgesia
- Readmission rates within 30 days of surgery
- Wound infection rates until the first follow up visit

5. Criteria for Inclusion of Subjects:

- Adult subjects aged 18 years or older
- Scheduled for elective posterior lumbar spinal fusion surgery between 1 and 3 levels

6. Criteria for Exclusion: Patients will be excluded if they have:

- Baseline cognitive deficits sufficient to make objective pain self-assessments unreliable in the estimation of the Study Investigators.
- Immunocompromised subject
- Coagulopathy
- Severe liver and renal dysfunction
- Preoperative neurological deficits
- The dura damage during surgery
- Inability to follow directions or comprehend the English language.
- Females who are pregnant
- Prisoners.
- Patient refusal to provide informed consent.
- Allergy to amide local anesthetics (lidocaine, bupivacaine, ropivacaine) Fentanyl allergy if the subject assigned epidural analgesia
- Hydromorphone allergy if the subject assigned IV PCA

7. Sources of Research Material

- Patient information including name, medical record number, Date of Birth, and contact information including phone number.
- Weight, height, BMI, medical and surgical history, Medication list
- Pain Scores
- Post-operative intravenous and oral opioid consumption (Morphine Equivalents).
- Patient satisfaction scores
- Evaluation of cognitive function/delirium
- Evaluation of Hospital Anxiety and Depression
- Length of stay
- Readmission rates
- Wound infection rates

8. Recruitment Methods and Consenting Process: Study will be introduced to potential subjects via phone call or MyChart message and the informed consent form will be emailed to interested subject for review. If subject want to be part of the study electronic consent will be obtained via DocuSign. If subject not reachable, they will be enrolled, and informed consent obtained in the preoperative clinic areas at UTSW Zale Lipshy University Hospital and the Spine Clinic during their preoperative surgery or anesthesiology visits. All subjects who meet the inclusion criteria based upon planned surgical intervention and who do not fulfill any of the

exclusion criteria will be approached regarding the study protocol. Therefore, all demographic groups in the surgical practice will be represented.

Consent Process– If subject wants to be part of the study, electronic consent will be obtained via DocuSign. If subject is not reachable, informed consent will be obtained during the surgical or anesthetic pre-operative visit by the research team once a subject is identified as being scheduled for the included spine surgery and not fulfilling any of the listed exclusion criteria.

Subject's Capacity to Give Legally Effective Consent – Subjects who do not have the capacity to given legally effective consent will not be included in the study.

Subjects will not be compensated for their participation in the study. Additionally, the study will require no additional hospital or clinic visits beyond those that are standard of care for the lumbar spinal fusion surgery, so there will be no anticipated additional expenses for travel time or lost wages.

9. Potential Risks: Vulnerable populations are excluded from this study. If a subject chooses not to participate in this study, they will receive IV PCA Hydromorphone and oral (by mouth) analgesics as is currently the standard of care at Zale Lipshy University Hospital.

- ***Risks of the Epidural Analgesia***

There is possibility of a non-working epidural catheter, infection, damage to nerves, arteries, and veins. An inadvertent placement of epidural catheter may result in systemic toxicity of local anesthetics (bupivacaine) inadequate pain relief, or epidural hematoma with neurological complications. Other side effect of epidural catheter placement includes dural puncture which may cause spinal headache. Epidural catheter will be placed by the surgeons under direct visualization at the end of the surgery. The surgical wound will be closed after ensuring the surgical field is dry and the catheter is not in the subarachnoid space. Subjects with dura damage during surgery will be excluded from the study.

1-**Infection**

Epidural catheter may cause infection such as meningitis. The incidence is very rare and increased after the 3 days of the epidural catheter placement. Infection will be monitored during postoperative period per hospital protocol. High risk subjects such as immunocompromised will not be enrolled to the study.

2-**Local anesthetic (bupivacaine) toxicity**

There is minimal risk of local anesthetic (bupivacaine) toxicity due to advert injection of local anesthetic into the blood vessel. If injected into a blood vessel, large amounts of local anesthetic (bupivacaine) can cause tinnitus, lightheadedness, dizziness, tachycardia, blurred vision, and numbness around mouth, seizures, hypotension, and even cardiac arrest. If it is happen appropriate supportive treatment will be given. The risk is high as the local anesthetic is infused in the raw surgical area that is hyperemic. The epidural catheter will be placed by an experienced surgeon under direct visualization and bupivacaine will be given a small amount via automatic pump, therefore the risk is minimal. The surgical wound will be closed after ensuring the surgical field is dry and the catheter is not in the subarachnoid space.

3- **Bleeding and Epidural Hematoma**

Epidural catheter placement may cause epidural bleeding and hematoma. There is also possibility of neurological damage as a consequence of epidural hematoma. Epidural catheter placement in patients with a history of use of anti-coagulant or anti-platelet therapies will be done following the American Society of Regional Anesthesia and Pain Medicine (ASRA) current guidelines—"Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines". Additionally, epidural catheters will be removed by the Acute Pain Service per protocol regarding patients who receive anti-coagulant or anti-platelet therapies post-operatively. These guidelines are followed to minimize the risk of epidural hematoma.

4**- Risk of Epidural Opioid (Fentanyl):**
Epidural fentanyl may cause common side effects of opioids including nausea, vomiting, pruritus (itching), drowsiness, urinary retention, and constipation. It may also decrease in breathing frequency (breathing rate <8 times/min), but low doses of fentanyl will be given very slowly and continuously. Because the doses of fentanyl will be given very low and investigators don't expect a decrease in the amount of respirations. The advert injection of fentanyl causes decreasing level of consciousness, hypotension, and respiratory depression.

5-**Risk of Epidural Bupivacaine**
Epidural bupivacaine may cause transient numbness or weakness, paralysis of lower extremities. Some degree of numbness and paresthesia expected but not motor block. Bupivacaine will be used low dose (0.0625%) to prevent development of motor block.

- **Risk of IV Patient-Controlled Analgesia:**

IV patient-controlled opioid analgesia is part of the standard treatment for post-operative pain after surgery. Patient will receive baseline infusion and additionally opioid as needed.

1-Risk of Intravenous Catheter:
If the intravenous cannula is not placed correctly, it may cause rupture of vessels and blood leaks into the surrounding tissue. Using this misplaced cannula also causes extravasation of IV fluid and the drug, which leads to edema, tissue damage, and pain. There is risk of insertion site infection which may lead phlebitis, cellulitis and even sepsis.

2-Risk of Hydromorphone:
Hydromorphone has side effects including nausea, vomiting, difficulty in urination, pruritus (itching), drowsiness, and constipation. It may also cause sedation and respiratory depression but low doses will be given very slowly and continuously.

- **Psychological Stress**

Some of the questions related to the study may make the subject feel uncomfortable. Subjects may refuse to answer any of the questions, or take a break or stop participation in the study at any time.

- **Loss of Confidentiality**

Any time information is collected; there is a potential risk of loss of confidentiality. Every effort will be made to keep subjects information confidential and secure as detailed below.

10. Costs to the Subject – We foresee no additional costs to the subjects. IV PCA is standard of care and epidural analgesia has been used for selected spine surgery cases at Zale University Hospital as a treatment option for postoperative pain management.

11. Subject Safety and Data Monitoring:
Since this is a single center study involving standard analgesic techniques, there is no safety monitoring board for this protocol. Data will be evaluated at the completion of the study to determine the efficacy and safety of epidural analgesia relative to control. Protocol violations and adverse events will be recorded and reported to the IRB during the study.

All unexpected or serious adverse events will be reported to the UTSW IRB office within 24 hours of their discovery. The PI will review aggregated adverse events after 25 subjects have been enrolled.

12. Procedures to Maintain Confidentiality:
All subjects will be identified by a numerical code (case # 01, case # 02…. etc.) during gathering and reporting the information. Study records will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law, subjects will not be identified by name, social security number, address, telephone number or any other direct personal identifier in study records disclosed outside of the UT Southwestern Medical Center. All research records will be locked in offices in the Departments of Anesthesiology and Pain Management, and Neurosurgery, , or stored on secure UT Southwestern computer servers. Only research staff listed as key personnel will be able to access these records.

13. Potential Benefit:
Subjects will not directly benefit from participation in this protocol other than receiving pain management from the Acute Pain Service (in both arms of the study). If the use of epidural analgesia is shown to be associated with better analgesia and postoperative outcomes, the potential benefits to future patients could be significant.

The results of this study will be used to optimize spine care at UTSW Zale University Hospital. Publication of study findings will contribute to the care of spine surgery patients in general.

Intended/Potential Use of Study Findings: The results of this study will be used to guide the analgesic care of patients undergoing lumbar spinal fusion surgery. Results will be published in a peer-reviewed medical journal.

14. Biostatistics
The primary outcome for this study is the post-operative pain score (Visual Analogue Scale) at 24 hours. The study is powered to detect a large effect size (Cohen's d = 0.8) in VAS pain score using a one-sided alternative with a type I error rate of 0.025 and power of 80%. To achieve this, a total of 52 patients are needed to be randomized in the two study groups. Assuming a 10% loss of patients before completion of surgery, a total of 58 patients will be randomized.

Continuous variables will be summarized using mean and standard deviation or median and inter-quartile range (IQR) while categorical variables will be summarized using frequency and

percentages. Comparison of the two study groups will be made using standard parametric or non-parametric statistical analyses as appropriate.

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